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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/202,054	12/07/1998	AUDREY GODDARD	P1154R2	2403

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/202,054	GODDARD ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30,48-50 and 54-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30 and 48-50 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

3Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/15/2004 has been entered.

Claims 28-30 and 48-50 and 54-57 are pending and under consideration.

Claim Rejections - 35 USC § 101 and §112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 28-30, 48-50 and 54 remain and newly submitted claims 55-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility, for reasons of record in the previous Office Action mailed 9/16/2002 at pages 2-4.

Applicants have newly submitted claims 55-57, which recite that the claimed antibody is an agonist or antagonist of NF-Kβ activation. The Examiner notes that (The Examiner also notes that this property was not enabled at the time the invention was made, such that if it had utility, it would still not be enabled under 35 U.S.C. §112, first paragraph.) Applicants allegations of utility pertain to the utility of drugs that modulate NF-Kβ activation caused by stimulation of IL-1, IL-6 and IL-8 receptors. However, it remains that even with the recitation of this property, the claims lack utility because NF-Kβ activation is a common response to the stimulation of a number of receptors. While it is true that inhibiting or stimulating NF-Kβ activation may have utility under certain circumstances, those circumstances are predicated on knowledge of involvement of the particular receptor that stimulates such signaling in a biological

process such as septic shock or warts. No such correlation has been disclosed for PRO285, and the discovery of such a correlation is considered to be part of the inventive process. The involvement of IL-1, -6 or -8 in the formation of warts, or in septic shock, is not predictive of the involvement of PRO285 in the same conditions. Furthermore, both IL-6 and IL-8 are regulated *by* NF-P9; while IL-6 also *induces* NF-P9, IL-8 is not known to, and the fact that both are regulated by such shows further evidence of the unpredictability of stimulating/inhibiting gene transcription at the NF-P9 level. Cytokines and chemokines (IL-1 being in the former group, IL-6 and IL-8 in the latter) are pleiotrophic molecules that have numerous and varied effects at the intracellular level. NF-P9 is an intranuclear signaling molecule, remote in the cascade from the initial step of binding of ligand to receptor at the cell surface. The antibodies that are claimed to simulate or inhibit NF-P9 activation would not do so directly, but rather via binding to the disclosed PRO285 molecule, which would then activate unknown intracellular signaling molecules, which then would activate NF-P9, although, as stated above, such was not known or predictable at the time the invention was made. It is also not known what other intracellular processes are affected by binding to PRO285, nor what the effect of binding of antibodies to PRO285 would be, *other* than the alleged activation of NF-P9. Accordingly, it remains that there is no utility for the claimed antibodies; rather, such are merely tools for an invitation to experiment to determine the properties of the disclosed PRO285 protein.

Applicants traversal of this rejection in the paper submitted 7/15/2004 have been fully considered but are not deemed persuasive.

Applicants repeatedly state in their argument that antibodies to PRO285 can be used to "modulate" NF-P9 signaling, however, the specification fails to teach how to do so, the claims require not such activity, and it is not clear what utility "modulation" of such signaling has if one has no idea in response to what stimulus such signaling occurs in nature. Applicants also repeatedly argue that stimulation of NF-P9 via PRO285 is useful for modulating the expression of IL-1, IL-6 and IL-8. This argument has been fully considered but is not deemed persuasive because it is not a substantial assertion; as stated above, it was not known or predictable at the time the invention was made that PRO285 would cause NF-P9 activation, and it is not known what other effects stimulation of PRO285 would have, such that the net effect of such

stimulation is unknown. Applicants allege that an article by Beutner et al. demonstrates that "reagents which induce the expression of IL-1, IL-6 and IL-8 are used in the topical treatment of warts". This argument has been fully considered but is not deemed persuasive because it is not clear to what treatment applicants are referring, as the article in question is a review of numerous treatment modalities for the treatment of genital warts, and the terms IL-1, IL-6 IL-8 and NF-P9 do not appear in any portion of the article.

At page 5, applicants reiterate their argument pertaining to the Bazan declaration, which was treated fully in the previous Office Action, to the following effect:

"The Bazan declaration filed 12/9/2003 under 37 CFR 1.132 is insufficient to overcome the rejection of claims 28-30, 48-50 and 54 35 U.S.C. §101 and §112 as set forth in the last Office action because:

Dr. Bazan refers to the specification at Figure 7B and page 7, lines 8-23 as showing that PRO285 has significant homology to the IL-1 receptor domain that is necessary for signaling via NF-P9 and that such would be predictive of NF-P9-mediated signaling by PRO285. This argument has been fully considered but is not deemed persuasive because Figure 7 shows an alignment of IL-1R with TLR2 in the region critical for IL-1R signaling. However, examination of Figure 7B reveals that six residues are indicated as being "essential for IL-1R signaling", and only three of those six are conserved in TLR2, which had not, as of the filing date of this application, been shown to signal via NF-P9. The declaration provides, for the first time, an alignment of the analogous region of PRO285 with both IL-1R and TLR2. The Examiner notes that of the six essential residues for IL-1R signaling, only *two* are conserved in PRO285. This amount of conservation is not persuasive of conservation of function. Therefore, based upon the information in the specification as originally filed, it does not appear that it would lead a person of ordinary skill in the art to the conclusion that PRO285 would be expected to have NF-P9 signaling activity.

At paragraphs 6-7, Dr. Bazan refers to an article by Rock et al., PNAS 95:588-593, previously of record, as teaching that it would be expected that PRO285 would signal via NF-P9. This argument has been fully considered but is not deemed persuasive

because while the Rock article clearly shows that five TLRs were evolutionarily related to the *Drosophila* Toll receptors, there is no clear indication that they would be expected to activate NF-P9, nor is there disclosure or discussion of PRO285. Declarant is arguing based on two steps removed from the data; the argument is that the function of IL-1R was known, that TLRs are similar to IL-1R and thus might share function, and that PRO285 is similar to TLRs. Further, mere signaling via NF-P9 would not be indicative of utility, for reasons cited below. While the Rock et al. paper states that the TLRs "could constitute an important and unrecognized component of innate immunity in humans", it also states, in the very next sentence, that "Intriguingly, the evolutionary retention of TLRs in vertebrates may indicate another role- akin to Toll in the dorsoventralization of the *Drosophila* embryo- as regulators of early morphogenetic patterning. Finally, the Rock paper does not disclose or discuss PRO285. Thus, based upon the Rock paper, it would seem that it was *not* predictable that PRO285 was involved in innate immunity via signaling via NF-P9, and that there were at least two very distinct ideas as to what the receptors disclosed therein might do. Finally, the fact that TLR4 was confirmed as signaling via NF-P9 does not have bearing on PRO285.

At paragraph 8, Dr. Bazan concludes that the person of ordinary skill in the art could, reading the specification, reasonably conclude that PRO285 signals via NF-P9, and that "antibodies to PRO285 could be made and used in accordance with routine techniques to modulate such activity." This argument has been fully considered but is not deemed persuasive because it is the opinion of the declarant, and is not supported by the facts and evidence of record, specifically: (a) As stated above, as essential residues of the IL-1R signaling domain are *not* conserved in PRO285, the Examiner does not agree with the assertion that the person of ordinary skill in the art, reading the specification as originally filed, would find it predictable that PRO285 signals via NF-P9. (b) The Rock publication indicates that TLRs *might* signal via NF-P9, or alternatively, *might* be involved in early morphogenic patterning, and does not disclose or discuss PRO285. (c) Even *if* it were predictable that PRO285 signaled via NF-P9, such is not a utility, in and of itself. NF-P9 is an intracellular signaling molecule. Without knowing any ligand for

PRO285 nor under what physiological circumstances the ligand binds to the receptor, the person of ordinary skill in the art would not know how to use the receptor for its NF-P9 signaling activity, that is, under what circumstances it would be desirable to stimulate or inhibit PRO285."

Also at page 5, applicants reiterate their argument of the Jurk reference, also dealt with in the previous office action, as follows:

Applicants have submitted with their response a paper by Jurk et al., (Nature Immunology 3:499, 2002), which demonstrates that even four years after the filing date of the instant application, the biological function of PRO285, by applicants assertion later designated TLR7, was unknown. Specifically, Jurk et al. teach that different TLRs signal in response to different stimuli; TLR2, 4 and 5 in response to peptidoglycan, lipopolysaccharide and flagellin, respectively, TLR6 in conjunction with TLR2 in response to lipoproteins from mycoplasma, TLR9 in response to bacterial DNA containing unmethylated CpG motifs, and TLR3 in response to dsRNA (see abstract). The Jurk paper goes on to state that "The natural ligands for TLR1, TLR7, TLR8 and TLR10 are not known, although a synthetic compound with antiviral activity has not been described as a ligand for TLR7. Thus, even four years after the filing date of the instant application, the role of TLR7, aka PRO285, was unknown, and the receptor was merely a subject for further research. This paper supports the Examiner's position that even *if* one were to accept, on the basis of the specification as originally filed, that PRO285 signals via NF-P9, that such does not confer any specific, substantial and credible utility upon the protein, nor upon antibodies that bind to it.

It remains that although applicants repeatedly state in their argument that antibodies to PRO285 can be used to "modulate" NF-P9 signaling, the specification fails to teach how to do so, most of the claims require not such activity, and it is not clear what utility "modulation" of such signaling has if one has no idea in response to what stimulus such signaling occurs in nature.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-30, 48-50 and 54 also remain, and new claims 55-57 are, rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants arguments of this rejection have been fully addressed above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28 and 48 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ruggeri et al., WO 91/09614.

Ruggeri et al. disclose a 19 residue peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 match; see the third peptide listed in claim 1. At page 19 and in claim 65, antibodies to such peptides are disclosed and claimed.

Applicants arguments have been fully considered but are not persuasive for reasons of record. It remains that according to "Exhibit C" submitted by applicants in their previous response, although antibodies raised against fragments generally have higher affinities for the fragment to which they were raised than to the native protein, (page 247)they nonetheless "show extensive cross-reactions with native proteins" (page 248). Further, at page 249, the reference goes on to state that "antipeptide antibodies have proved to be very powerful reagents", and can be used to immunoprecipitate previously unisolated native proteins, to isolate previously

8unidientified gene products of new genes, and in detecting post-translational processing, are useful in probing structure-function relationships, and can be used to block protein binding. Accordingly, the reference provided by applicants teaches that one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285. Since the Office does not have the facilities for examining and comparing applicants' antibodies with those of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:.

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ruggeri et al., WO 91/09614, in view of Coughlin, U.S. Patent Number 5,256,766 for reasons of

record. Applicants argument of Ruggeri is found not persuasive, for reasons cited above. Applicants have presented no separate argument of the obviousness rejection.

Claims 50 and 54 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ruggeri et al., WO 91/09614, in view of Coughlin, U.S. Patent Number 5,256,766, and further in view of U.S. Patent Number 4,946,778 (Ladner et al.) for reasons of record. Applicants argument of Ruggeri is found not persuasive, for reasons cited above. Applicants have presented no separate argument of the obviousness rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

10/25/2004